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(54) 4,5-Dihydroimidazol-2-yl Amino Substituted Isoquinolines

(57) New Isoquinoline derivatives of
the general formula:



wherein R₁ represents a hydrogen atom or a hydroxylalkyl radical containing 1 to 4 carbon atoms, the imidazol-2-ylamino group is attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus,

and the symbols R₂ and R₃, which have the same or different significances, are attached to carbon atoms in the remaining positions of the isoquinoline nucleus and each represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkoxyalkyl group in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, or a dialkylamino group in which each alkyl radical contains 1 to 4 carbon atoms, are useful as anti-hypertensive agents.

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SPECIFICATION
Isoquinoline Derivatives

This invention relates to new therapeutically useful isoquinoline derivatives, to processes for

5 their preparation and pharmaceutical compositions containing them.

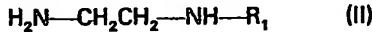
The new isoquinoline derivatives of the present invention are those of the general formula:



10 [wherein R₁ represents a hydrogen atom or a hydroxyalkyl radical containing 1 to 4 carbon atoms (e.g. 2-hydroxyethyl), it being understood that the imidazolin-2-ylamino group can be located in the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus, and the symbols R₂ and R₃, which have the same or different significances, are attached to carbon atoms in the remaining positions of the isoquinoline nucleus and each represents a hydrogen or halogen (e.g. chlorine or bromine) atom or an alkyl radical containing 1 to 4 carbon atoms (e.g. methyl), an alkoxy radical containing 1 to 4 carbon atoms (e.g. methoxy), an alkoxyalkyl group in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms (e.g. 25 methoxymethyl), an alkylthio radical containing 1 to 4 carbon atoms (e.g. methylthio) or a dialkylamino group in which each alkyl radical contains 1 to 4 carbon atoms (e.g. dimethylamino)] and acid addition salts thereof.

30 Preferably R₁ and R₂ are as hereinbefore defined, and R₃ represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms or an alkylthio radical containing 1 to 4 carbon atoms.

According to a feature of the invention, the 35 isoquinoline derivatives of general formula (I) are prepared by the process which comprises reacting an ethylenediamine of the general formula:



(wherein R₁ is as hereinbefore defined) with an 40 isoquinoline derivative of the general formula:



wherein R₂ and R₃ are as hereinbefore defined and Z attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus represents (i) a 2-45 alkylisothioureido group of the general formula:



or (ii) an (alkylthio)-thiocarbonylamino group of the general formula:

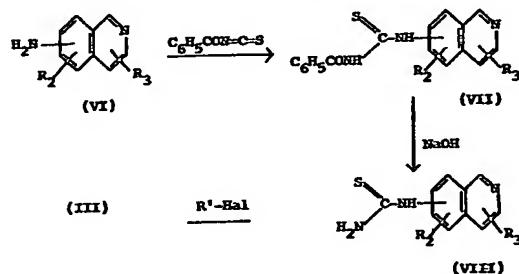


50 [wherein R' in general formulae (IV) and (V) represents an alkyl radical containing 1 to 4 carbon atoms], or (iii) the isothiocyanato radical.

When Z represents a 2-alkylisothioureido group of general formula (IV), the reaction is

55 generally carried out by employing an excess of the ethylenediamine of general formula (II), preferably 3 mols per mol of isoquinoline derivative of general formula (III), and by operating in an inert organic solvent, such as an 60 alcohol containing 1 to 4 carbon atoms (e.g. methanol, ethanol or butanol) at a temperature between 40°C and the reflux temperature of the reaction mixture, for a period of time which can vary from 1 hour to 48 hours depending on the 65 reactivity of the starting materials employed. The compound of general formula (III) is preferably used in the form of a salt with an inorganic or organic acid, such as the hydrochloride, hydrobromide, hydroiodide or sulphate.

70 The 2-alkylisothioureidoisoquinolines of general formula (III) [viz. wherein Z is a group of formula (IV)] can be obtained in three stages from the corresponding aminoisoquinolines, 75 analogously to the method described by B. Rouot *et al.*, *J. Med. Chem.*, **19**, 1049 (1976), i.e. in accordance with the following scheme:



wherein the various symbols are as hereinbefore defined.

80 When in general formula (III) Z represents an (alkylthio)-thiocarbonylamino group of general formula (V), the reaction is generally carried out in an organic solvent, such as ethanol, at the reflux temperature of the reaction mixture and 85 advantageously in the presence of a mercuric derivative such as mercuric oxide.

The dithiocarbamates of general formula (III) [viz. wherein Z is a group of formula (V)] can be obtained by reacting an alkylating agent, such as 90 an alkyl halide (e.g. methyl iodide) or an alkyl sulphate (e.g. dimethyl sulphate), with a dithiocarbamic acid salt of the general formula:



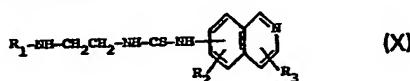
wherein R₂ and R₃ are as hereinbefore defined and 95 R'' represents an alkyl radical containing 1 to 4 carbon atoms, preferably the ethyl radical. The reaction is generally carried out in an organic solvent, such as acetonitrile, at a temperature between 20° and 50°C.

100 The dithiocarbamic acid salts of general

formula (IX) can be obtained by reacting carbon disulphide, in the presence of a tertiary amine of the general formula $N(R'')_3$, wherein R'' is as hereinbefore defined, with an aminoisoquinoline of general formula (VI), the reaction being carried out in an organic solvent, such as acetonitrile, at a temperature of about 20°C.

When in general formula (III), Z represents the isothiocyanato radical, the reaction is generally carried out in an organic solvent, such as tetrahydrofuran or ethanol, or a mixture of organic solvents, at the boiling point of the reaction mixture and advantageously in the presence of a mercuric derivative such as mercuric oxide.

In order to carry out this process, it is possible to prepare, as an intermediate, a thioureidoisoquinoline of the general formula:



(wherein R_1 , R_2 and R_3 are as hereinbefore defined) by reacting an ethylenediamine of general formula (II) with an isothiocyanatoisoquinoline of the general formula (III) [viz. wherein Z is the isothiocyanato radical] in an organic solvent, such as ethanol, acetonitrile or methylene chloride, at a temperature of about 20°C, and then to cyclise the intermediate of general formula (X) in order to obtain an isoquinoline derivative of general formula (I), the reaction being carried out in an organic solvent, such as ethanol, at a temperature between 20°C and the reflux temperature of the reaction medium, preferably in the presence of a mercuric derivative such as mercuric oxide.

The isothiocyanatoisoquinolines of general formula (III) [viz. wherein Z is the isothiocyanato radical] can be obtained by reacting thiocarbonyldiimidazole with an aminoisoquinoline of general formula (VI), the reaction being carried out in an organic solvent, such as methylene chloride or acetonitrile, at a temperature between 0° and 40°C.

The aminoisoquinolines of the general formula (VI) can be obtained by operating analogously to the method described by F. A. French *et al.*, *J. Med. Chem.*, 13, (6), 117 (1970) or by E. Brown, *J. Org. Chem.*, 42, 3208 (1977).

The isoquinoline derivatives of general formula (I) wherein R_1 represents a hydrogen atom or a hydroxyalkyl radical containing 1 to 4 carbon atoms, it being understood that the imidazolin-2-ylamino group is attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus, and one of the symbols R_2 and R_3 represents a halogen atom, preferably a chlorine or bromine atom, and the other symbol represents a hydrogen or halogen atom or an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkoxyalkyl group in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms or a dialkylamino group in which each alkyl radical contains 1 to 4

carbon atoms, can also be obtained by another process according to the invention which comprises reacting a halogenating agent with an isoquinoline derivative of general formula (I) wherein R_1 is as defined above and one of the symbols R_2 and R_3 represents a hydrogen atom and the other represents a hydrogen or halogen atom or an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkoxyalkyl group in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms or a dialkylamino group in which each alkyl radical contains 1 to 4 carbon atoms, it being understood that, when the symbols R_2 and R_3 each represent a hydrogen atom, two halogen atoms can be attached to the isoquinoline nucleus.

The halogenating agent which is preferably used is chlorine or bromine, the reaction being carried out in an organic solvent, such as acetic acid, or an alkali metal hypochlorite in a concentrated acid medium (e.g. hydrochloric acid), in the presence of zinc chloride, at a temperature between 0° and 40°C.

The halogen atom(s) is (or are) preferably attached in the electrophilic position(s) of the isoquinoline nucleus and more particularly in the *ortho* or *para* position relative to the imidazolin-2-ylamino group.

If the reaction produces a mixture of halogenated products, they are subsequently separated by one of the fractionation methods applicable to this type of compound, in particular by fractional crystallisation or chromatography.

The isoquinoline derivatives of general formula (I) obtained by the aforescribed processes can be purified by physical methods such as crystallisation or chromatography, or by chemical methods such as the formation of salts, crystallisation of the salts and decomposition of them in an alkaline medium. In carrying out the said chemical method the nature of the anion of the salt is immaterial, the only requirement being that the salt must be well-defined and readily crystallisable.

The isoquinoline derivatives of general formula (I) may be converted by known methods into acid addition salts. The acid addition salts may be obtained by the action of acids on the isoquinoline derivatives in appropriate solvents. As organic solvents there may be used alcohols, ethers, ketones or chlorinated hydrocarbons. The salt which is formed is precipitated, if necessary after concentration of the solution, and is isolated by filtration or decantation.

By the term "known methods" as used in this specification is meant methods heretofore used or described in the chemical literature.

The isoquinoline derivatives of the present invention and their acid addition salts possess useful pharmacological properties. They have shown themselves to be particularly active as regulators for the cardiovascular system. At doses between 0.01 and 5 mg/kg animal body weight,

administered orally, they lower the arterial pressure in spontaneously hypertensive rats (S.H.R.) of the Okamoto-Oaki strain. The use of spontaneously hypertensive rats for studying anti-hypertensive products is described by J. L. Roba, *Lab. Anim. Sci.*, 26, 305 (1976).

Furthermore, the isoquinoline derivatives of this invention have no sedative action at doses at which they are active as anti-hypertensive agents, 10 in particular using the technique of the potentiation of the narcoses induced by pentobarbital in rats.

Furthermore, the isoquinoline derivatives of general formula (I) exhibit a relatively low toxicity. 15 In mice, their 50% lethal dose (LD_{50}) is generally greater than 150—200 mg/kg animal body weight, administered orally.

For therapeutic purposes the isoquinoline derivatives of general formula (I) are employed as such or in the form of non-toxic salts, i.e. salts containing anions which are relatively innocuous to the animal organism in therapeutic doses of the salts (such as hydrochlorides, sulphates, nitrates, phosphates, acetates, propionates, succinates, 20 benzoates, fumarates, maleates, tartrates, theophylline-acetates, salicylates, phenolphthalinates and methylene-bis- β -hydroxynaphthoates) so that the beneficial physiological properties inherent in the bases are 25 not vitiated by side effects ascribable to the anions.

Of outstanding value are the isoquinoline derivatives of general formula (I) wherein R_1 represents a hydrogen atom, the imidazolin-2-ylamino radical being located in the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus, and the symbols R_2 and R_3 , which have the same or different significances, each 30 represents a hydrogen or halogen atom or an alkyl radical containing 1 to 4 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms. Preferably the imidazolin-2-ylamino group of the isoquinoline derivatives of the general formula (I) is attached to the 4-, 5- or 8-position of the 35 isoquinoline nucleus.

The following compounds 4-(4-5-dihydroimidazol-2-yl)aminoisoquinoline, 8-(4-5-dihydroimidazol-2-yl)-aminoisoquinoline, 8-(4-5-dihydroimidazol-2-yl)amino-1-methylisoquinoline, 8-(4-5-dihydroimidazol-2-yl)amino-7-methylisoquinoline and 8-(4-5-dihydroimidazol-2-yl)amino-5-methylisoquinoline 45 and their acid addition salts, are of outstanding interest.

50 The following Examples illustrate the invention.

Example 1

A mixture of 4-(2-methylisothioureido)isoquinoline hydroiodide (34.5 g) and ethylenediamine (27.0 g) in ethanol (250 cc) is heated under reflux for 7 hours. After concentration of the resulting suspension under reduced pressure (20 mm Hg), the residue is taken up in N aqueous sodium hydroxide solution (100 cc) and chloroform (100 cc). The resulting

65 suspension is filtered and the cake is washed with distilled water (100 cc) and dried under reduced pressure (0.1 mm Hg). The resulting solid is dissolved in boiling dimethylformamide (175 cc). The hot solution is filtered, the filtrate is then

70 cooled to a temperature of about 0°C and this temperature is maintained for 1 hour. The resulting crystals are filtered off. After drying under reduced pressure (0.1 mm Hg) at 20°C for 15 hours and then under the same vacuum at 75 50°C for 1 hour 4-(4,5-dihydroimidazol-2-yl)-aminoisoquinoline (13.4 g), melting at 247°—248°C, is obtained.

The 4-(2-methylisothioureido)isoquinoline hydroiodide can be prepared in the following manner:

80 A suspension of 4-thioureidoisoquinoline (56 g) and methyl iodide (41.2 g) in methanol (750 cc) is heated under reflux for 45 minutes. After concentration of the resulting solution under reduced pressure (20 mm Hg), the residue is

85 crystallised from acetone (250 cc). The crystals are filtered off, washed with acetone (50 cc) and dried for 15 hours under reduced pressure (0.2 mm Hg) at 20°C. 4-(2-

90 methylisothioureido)isoquinoline hydroiodide (76.8 g), melting at 184°—186°C, is thus obtained.

The 4-thioureidoisoquinoline can be prepared in the following manner:

95 4-(3-benzoylthioureido)isoquinoline (93.5 g) in ethanol (700 cc) and 10 N aqueous sodium hydroxide solution (91 cc) are heated under reflux for 15 minutes. After cooling, the crystals are

100 filtered off and washed with ice-cooled ethanol (300 cc). The filtrate is concentrated under reduced pressure (20 mm Hg), the residue is dissolved in distilled water (500 cc) and the resulting solution is acidified by adding acetic acid until the pH is 5—6. The resulting crystals are

105 filtered off, washed with distilled water (300 cc) and dried for 15 hours under reduced pressure (0.2 mm Hg) at 20°C. 4-thioureidoisoquinoline (53.7 g), which melts at 235°—236°C, is thus obtained.

110 The 4-(3-benzoylthioureido)isoquinoline can be prepared in the following manner:

Benzoyl chloride (53.6 g) is added, in the course of 10 minutes, to a solution of acetone (100 cc) and ammonium thiocyanate (29.2 g),

115 which has been heated to 45°C beforehand, and the mixture is then heated under reflux for 10 minutes. A solution of 4-aminoisoquinoline (55.2 g) in acetone (150 cc) is added, in the course of 10 minutes, to the suspension which is kept under reflux, and reflux is then maintained for 1 hour 30 minutes. The suspension is then cooled, distilled water (750 cc) is added and the resulting crystals are filtered off and washed with distilled water (300 cc). After drying for 45 hours under reduced pressure (0.2 mm Hg) at 20°C, 4-(3-

120 benzoylthioureido)isoquinoline (93.6 g), which melts at 210°—211°C, is obtained.

4-aminoisoquinoline used as starting material can be prepared in accordance with the method

described by I. G. Hinton, J. Chem. Soc., 599 (1959).

Example 2

A mixture of 5-(2-

5 methylisothioureido)isoquinoline hydroiodide (11.7 g) and ethylenediamine (6.1 g) in ethanol (85 cc) is heated under reflux for 15 hours. After concentration of the resulting solution under reduced pressure (20 mm Hg), the residue is taken up in N aqueous sodium hydroxide solution (120 cc) and extraction is carried out with chloroform (500 cc). After drying over sodium sulphate, the chloroform solution is concentrated under reduced pressure (20 mm Hg), the residue is taken up in boiling cyclohexane (1200 cc), the mixture is filtered hot and the insoluble product is dried under reduced pressure (0.1 mm Hg). This product is dissolved in an N aqueous solution of hydrochloric acid (70 cc) and distilled water (40 cc), the solution is decolourised with animal charcoal (0.2 g), the mixture is filtered and the filtrate is rendered alkaline at a temperature of about 0°C by adding N aqueous sodium hydroxide solution (70 cc). The solid is filtered off, washed with distilled water (60 cc) and dried under reduced pressure (0.1 mm Hg) for 22 hours at 20°C. 5-(4,5-dihydroimidazol-2-yl)aminoisoquinoline (5.0 g), melting at 191°—192°C, is thus obtained.

25 The starting materials can be prepared by following the procedure of Example 1. Thus, 5-(2-methylisothioureido)isoquinoline hydroiodide (19 g), which melts at 240°—245°C with decomposition, is obtained by heating 5-thioureidoisoquinoline (18.3 g) and methyl iodide (41.0 g) in acetone (180 cc); 5-thioureidoisoquinoline (45.1 g), which melts at 262°—264°C, is obtained by hydrolysing 5-(3-benzoylthioureido)isoquinoline (127.5 g) in ethanol (1,245 cc) and 10 N aqueous sodium hydroxide solution (124.5 cc), and 5-(3-benzoylthioureido)isoquinoline (128.3 g), which melts at 233°—234°C, is obtained from 5-aminoisoquinoline (72.1 g), benzoyl chloride (70.3 g) and ammonium thiocyanate (38.1 g) in acetone (475 cc).

30 5-aminoisoquinoline used as starting material can be prepared in accordance with the method described by F. Misani, J. Org. Chem., 10, 347 (1945).

Example 3

3-methyl-5-(2-methylisothioureido)isoquinoline hydroiodide (35.9 g) and ethylenediamine (18.0 g) in ethanol (250 cc) are heated under reflux for 7 hours. After concentration of the reaction mixture under reduced pressure (20 mm Hg), the residue is taken up in distilled water (100 cc). The resulting crystals are filtered off, washed with water (100 cc) and dried under reduced pressure (0.2 mm Hg). The resulting product is dissolved in isopropanol (250 cc) under reflux, the solution is clarified with animal charcoal (1 g) and the

65 mixture is filtered hot. The resulting solution is cooled to a temperature of about 0°C with an ice-bath for one hour and the crystals are filtered off and washed with isopropanol (100 cc). After drying under reduced pressure (0.2 mm Hg) at 20°C for 15 hours and then at 45°C for 2 hours, 5-(4,5-dihydroimidazol-2-yl)-amino-3-methylisoquinoline (13.2 g), melting at 202°—204°C, is obtained.

70 The starting materials can be prepared by following the procedure of Example 1. Thus, 3-methyl-5-(2-methylisothioureido)isoquinoline hydroiodide (60.5 g), which melts at 240°—242°C with decomposition, is obtained by heating 3-methyl-5-thioureidoisoquinoline (39 g) and methyl iodide (28.4 g) in methanol (700 cc); 3-methyl-5-thioureidoisoquinoline (39 g), which melts at about 280°C, is obtained by hydrolysing 5-(3benzoylthioureido)-3-methylisoquinoline (65 g) with 10 N aqueous sodium hydroxide solution (60 cc) in ethanol (850 cc), and 5-(3-benzoylthioureido)-3-methylisoquinoline (65 g), which melts at 203°—204°C, is obtained from 5-amino-3-methylisoquinoline (35 g), benzoyl chloride (31 g) and ammonium thiocyanate (16.8 g) in acetone (265 cc).

80 5-amino-3-methylisoquinoline can be prepared in accordance with the method described by N. P. Buu Hoi, J. Chem. Soc., 3924 (1964).

Example 4

5-(2-methylisothioureido)isoquinoline hydroiodide (20.7 g) and 2-(2-hydroxyethyl)aminoethylamine (18.8 g) in ethanol (240 cc) are heated under reflux for 24 hours. The solvent is driven off under reduced pressure (20 mm Hg) and the residue is then extracted with chloroform (600 cc) and N aqueous sodium hydroxide solution (100 cc). The chloroform extract is washed with distilled water (600 cc) and dried over sodium sulphate, the mixture is filtered and the filtrate is concentrated under reduced pressure (20 mm Hg). The resulting residue is dissolved in ethanol (200 cc), the solution is clarified with animal charcoal (0.2 g) and the mixture is filtered. A 3.6 N solution of hydrogen chloride gas in diethyl ether (40 cc) is added to the filtrate. The mixture is stirred for 5 hours at 20°C and the resulting crystals are filtered off and washed with ethanol (85 cc). After drying under reduced pressure (20 mm Hg) at 20°C for 20 hours, 5-[1-(2-hydroxyethyl)-4,5-dihydroimidazol-2-yl]aminoisoquinoline (15.2 g) is obtained in the form of the dihydrochloride, which melts at 250°—255°C with decomposition.

110 2-(2-hydroxyethyl)aminoethylamine can be prepared according to R. Knorr, Ber., 35, 4470 (1902).

Example 5

3,4-dimethyl-5-(2-methylisothioureido)isoquinoline hydroiodide (8.6 g) and ethylenediamine (5.6 g) in ethanol (80 cc) are heated under reflux for 38 hours. After concentration of the reaction mixture under

+ imidazol
not a urea

reduced pressure (20 mm Hg), the residue is taken up in distilled water (50 cc). The resulting crystals are filtered off, washed with distilled water (60 cc) and dried under reduced pressure (0.2 mm Hg). The solid obtained is dissolved in acetonitrile (320 cc) under reflux, the solution is clarified with animal charcoal (1 g) and the mixture is filtered hot. The resulting solution is cooled in an ice-bath for 1 hour and the crystals formed are filtered off and washed with acetonitrile (60 cc). After drying under reduced pressure (0.2 mm Hg) for 15 hours at 20°C and then for 2 hours at 50°C, 5-(4,5-dihydroimidazol-2-yl)amino-3,4-dimethylisoquinoline (3.3 g), melting at 220°—221°C, is obtained.

The starting materials can be obtained by following the procedure of Example 1. Thus, 3,4-dimethyl-5-(2-methylisothioureido)isoquinoline hydroiodide (8.6 g), which melts at 174°—176°C, is obtained by heating 3,4-dimethyl-5-thioureidoisoquinoline (8.8 g) and methyl iodide (6.6 g) in methanol (175 cc); 3,4-dimethyl-5-thioureidoisoquinoline (8.8 g), which melts at 248°—250°C, is obtained by hydrolysing 5-(3-benzoylthioureido)-3,4-dimethylisoquinoline (14.4 g) with 10 N aqueous sodium hydroxide solution (13.7 cc) in ethanol (170 cc), and 5-(3-benzoylthioureido)-3,4-dimethylisoquinoline (14.4 g), which melts at 203°—204°C, is obtained from 5-amino-3,4-dimethylisoquinoline (8.6 g), benzoyl chloride (7.7 g) and ammonium thiocyanate (4.2 g) in acetone (130 cc).

The 5-amino-3,4-dimethylisoquinoline can be prepared, analogously to 5-amino-3-methylisoquinoline, from 3,4-dimethylisoquinoline by nitration and then reduction in accordance with the method of N.P. Buu Hoi, J. Chem. Soc., 3924 (1964).

40 Example 6

7-(2-methylisothioureido)isoquinoline hydroiodide (38.5 g) and ethylenediamine (33.1 g) in ethanol (250 cc) are heated under reflux for 2 hours. After cooling, 5 N aqueous sodium hydroxide solution (25 cc) is added, the mixture is cooled in an ice-bath for 30 minutes and the resulting crystals are filtered off and washed with 90% ethanol (30 cc). The resulting product is dissolved in dimethylformamide (250 cc) at 100°C, the solution is clarified with animal charcoal (0.1 g), the mixture is filtered hot, the filtrate is cooled to about 20°C with a water-bath and then to a temperature of about 0°C with an ice-bath and this temperature is maintained for one hour. The crystals which are formed are filtered off, washed with dimethylformamide (30 cc) and dried under reduced pressure (0.2 mm Hg) at 20°C for 15 hours and then under the same vacuum at 50°C for one hour. 7-(4,5-dihydroimidazol-2-yl)aminoisoquinoline (9.9 g) melting at 262°—263°C, is thus obtained.

The starting materials can be obtained by following the procedure of Example 1. Thus, 7-(2-methylisothioureido)isoquinoline hydroiodide

65 (38.6 g), which melts at 198°—200°C, is obtained by heating 7-thioureidoisoquinoline (44.1 g) and methyl iodide (34.0 g) in methanol (620 cc); 7-thioureidoisoquinoline (44.2 g) which melts at 258°—259°C, is obtained by hydrolysing 7-(3-benzoylthioureido)isoquinoline (68.1 g) in ethanol (500 cc) and 10 N aqueous sodium hydroxide solution (67 cc), and 7-(3-benzoylthioureido)isoquinoline (68.2 g), which melts at 222°—223°C, is obtained from 7-aminoisoquinoline (42.2 g), benzoyl chloride (41.2 g) and ammonium thiocyanate (22.3 g) in acetone (200 cc) and dimethylformamide (50 cc). 7-aminoisoquinoline used as starting material can be prepared in accordance with the method described by R. Robinson, J. Amer. Chem. Soc., 69, 1939 (1947).

Example 7

A mixture of 8-(2-methylisothioureido)isoquinoline hydroiodide (34.5 g) and ethylenediamine (28.8 g) in methanol (250 cc) is heated under reflux for 16 hours. The solvent is then evaporated off under reduced pressure (20 mm Hg) and the residue is extracted with chloroform (700 cc) and N aqueous sodium hydroxide solution (250 cc). The solvent is again evaporated off under reduced pressure (20 mm Hg), the residue is dissolved in boiling chloroform (90 cc), the solution is clarified with animal charcoal (0.1 g), the mixture is filtered hot, the filtrate is cooled to a temperature of about 0°C and this temperature is maintained for 2 hours. The crystals which have appeared are filtered off, washed with diisopropyl ether (50 cc) and dried under reduced pressure (0.2 mm Hg).

100 The resulting solid is dissolved in boiling acetonitrile (200 cc), the solution is then cooled to a temperature of about 0°C and this temperature is maintained for 3 hours. The suspension obtained is filtered and the resulting crystals are washed with acetonitrile (30 cc) and dried under reduced pressure (0.2 mm Hg) at 20°C for 15 hours and then at 50°C for one hour. 8-(4,5-dihydroimidazol-2-yl)aminoisoquinoline (4.9 g), melting at 225°—226°C, is thus obtained.

The starting materials can be obtained by following the procedure indicated in Example 1. Thus, 8-(2-methylisothioureido)isoquinoline hydroiodide (31.2 g), which melts at 227°—228°C, is obtained by heating 8-thioureidoisoquinoline (32 g) and methyl iodide (24.6 g) in methanol (350 cc); 8-thioureidoisoquinoline (32.1 g), which melts at 263°—265°C, is obtained by hydrolysing 8-(3-benzoylthioureido)isoquinoline (54.2 g) in ethanol (400 cc) and 10 N aqueous sodium hydroxide solution (53 cc), and 8-(3-benzoylthioureido)isoquinoline (54.3 g), which melts at 239°—240°C, is obtained from 8-aminoisoquinoline (30 g), benzoyl chloride (29.3 g) and ammonium thiocyanate (15.9 g) in acetone (350 cc).

8-aminoisoquinoline can be prepared in

accordance with the method described by Y. Ahmad, J. Chem. Soc., 3882 (1961).

Example 8

A mixture of 6-(2-

5 methylisothioureido)isoquinoline hydroiodide (9.0 g) and ethylenediamine (6.6 g) in ethanol (90 cc) is heated under reflux for 7 hours. The solvent is then evaporated off under reduced pressure (20 mm Hg), the residue is taken up in distilled water (100 cc) and the mixture is cooled to about 0°C. This temperature is maintained for 2 hours. The crystals which have appeared are filtered off, washed with distilled water (75 cc) and dried under reduced pressure (0.2 mm Hg) for 15 hours.

10 The resulting solid is dissolved in isopropanol (100 cc) under reflux, the solution is clarified with animal charcoal (0.5 g), the mixture is filtered hot, the resulting solution is cooled to a temperature of about 0°C and this temperature is maintained

15 for one hour. The resulting crystals are filtered off, washed with isopropanol (15 cc) and dried under reduced pressure (0.2 mm Hg) at 20°C for 15 hours and then under the same vacuum at 50°C for 2 hours. 6-(4,5-dihydroimidazol-2-yl)aminoisoquinoline (1.85 g), melting at 245°—246°C, is thus obtained.

The starting materials can be obtained by following the procedure of Example 1. Thus, 6-(2-methylisothioureido)isoquinoline hydroiodide (9.1 g), which melts at about 200°C, is obtained by heating 6-thioureidoisoquinoline (6.0 g) with methyl iodide (5 g) in methanol (140 cc); 6-thioureidoisoquinoline (6.1 g), which melts at 260°—262°C, is obtained by hydrolysing 6-(3-benzoylthioureido)isoquinoline (14 g) in ethanol (170 cc) and 10 N aqueous sodium hydroxide solution (13.7 cc), and 6-(3-benzoylthioureido)isoquinoline (18 g), which melts at 208°—210°C, is obtained from 6-aminoisoquinoline (17.3 g), benzoyl chloride (18.3 g) and ammonium thiocyanate (9.9 g) in acetone (70 cc).

40 6-aminoisoquinoline can be obtained in accordance with the method described by R. Manske, J. Amer. Chem. Soc., 72, 4997 (1950).

Example 9

A mixture of 6-chloro-5-(2-methylisothioureido)isoquinoline hydroiodide (22.7 g) and ethylenediamine (15 g) in ethanol (230 cc) is heated under reflux for 20 hours. The solvent is then evaporated off under reduced pressure (20 mm Hg) and the residue is extracted with chloroform (350 cc) and water (450 cc). The organic extract is washed with distilled water (300 cc), clarified with animal charcoal (1 g) and dried over sodium sulphate (30 g), the mixture is filtered and the solvent is then evaporated off under reduced pressure. The residue is dissolved in boiling trichloroethylene (250 cc), the solution is clarified with animal charcoal (1 g) and filtered, and the filtrate is cooled at a temperature of about 0°C for one hour. The crystals which have appeared are filtered off, washed with

65 trichloroethylene (45 cc) and dried under reduced pressure (0.2 mm Hg) at 20°C for 15 hours. The resulting solid is extracted with distilled water (25 cc), an N solution of hydrochloric acid (25 cc) and diethyl ether (90 cc). Animal charcoal (1 g) is added to the aqueous extract, the mixture is filtered, the filtrate is cooled to a temperature of about 0°C and the cold hydrochloride solution is rendered alkaline by adding 10 N aqueous sodium hydroxide solution (2.6 cc). The resulting crystals formed are filtered off, washed with water (50 cc) and dried under reduced pressure (0.2 mm Hg) at 20°C for 15 hours and then under the same vacuum at 50°C for 3 hours. 6-chloro-5-(4,5-dihydroimidazol-2-yl)aminoisoquinoline (2.2 g), melting at 156°—158°C, is thus obtained.

70 The starting materials can be obtained by following the procedure of Example 1. Thus, 6-chloro-5-(2-methylisothioureido)isoquinoline hydroiodide (44.0 g), which melts at about 220°C, is obtained by heating 6-chloro-5-thioureido-isoquinoline (41.3 g) with methyl iodide (27 g) in methanol (700 cc); 6-chloro-5-thioureidoisoquinoline (41.4 g), which melts at 170°—172°C, is obtained by hydrolysing 5-(3-benzoylthioureido)-6-chloroisoquinoline (55.7 g),

75 90 in ethanol (650 cc) and 10 N aqueous sodium hydroxide solution (52 cc); 5-(3-benzoylthioureido)-6-chloroisoquinoline which melts at 206°—208°C, is obtained from 5-amino-6-chloroisoquinoline (30.5 g), benzoyl chloride (26.7 g) and ammonium thiocyanate (14.5 g) in acetone (470 cc); 5-amino-6-chloroisoquinoline (29.0 g), which melts at 118°—120°C, is obtained by reducing 6-chloro-5-nitroisoquinoline (42 g) with iron powder (48.3 g) in water (525 cc), and 6-chloro-5-nitroisoquinoline (42.1 g), which melts at 135°—136°C, is obtained by nitrating 6-chloroisoquinoline (34 g) with potassium nitrate (46.2 g) in concentrated sulphuric acid (140 cc).

95 100 105 6-chloroisoquinoline can be obtained in accordance with the method described by G. Favini, Gazz. Chim. Ital., 89, 2222 (1959).

Example 10

6-methoxy-5-(2-

110 methylisothioureido)isoquinoline hydroiodide (6.9 g) and ethylenediamine (4.3 g) in ethanol (70 cc) are heated under reflux for 17 hours. After cooling, the solution is concentrated under reduced pressure (20 mm Hg) at 20°C and the residue is taken up in distilled water (80 cc), whilst stirring for 2 hours at 0°C. After filtration, the insoluble material is washed with distilled water (85 cc) and then dried under reduced pressure (0.1 mm Hg) at 20°C. The resulting solid is dissolved in boiling acetonitrile (110 cc) in the presence of decolourising charcoal (0.6 g). After hot filtration, the filtrate is cooled for 1 hour at 0°C. The product which precipitates is filtered off, washed with acetonitrile (25 cc) and then dried under reduced pressure (0.1 mm Hg) at 20°C for 20 hours.

The resulting solid (1.05 g) is dissolved in

boiling acetonitrile (80 cc) in the presence of decolourising charcoal (0.2 g). After hot filtration, the filtrate is cooled for 2 hours at 20°C. The product which precipitates is filtered off, washed with acetonitrile (15 cc) and then dried under reduced pressure (0.2 mm Hg) at 20°C. 5-(4,5-dihydroimidazol-2-yl)amino-6-methoxyisoquinoline (0.85 g), melting at 204°—205°C, is thus obtained.

6-methoxy-5-(2-methylthioureido)isoquinoline hydroiodide can be obtained from 6-methoxyisoquinoline. To this effect, 6-methoxy-5-(2-methylthioureido)isoquinoline hydroiodide (7 g), which melts at 240°C (with decomposition), is prepared by heating 6-methoxy-5-thioureidoisoquinoline (22 g) and methyl iodide (15.6 g) in methanol (400 cc); 6-methoxy-5-thioureidoisoquinoline (22 g), which melts at 170°—172°C, is prepared by heating 5-(3-benzoylthioureido)-6-methoxyisoquinoline (36.8 g) in ethanol (410 cc) and 10 N aqueous sodium hydroxide solution (33 cc); 5-(3-benzoylthioureido)-6-methoxyisoquinoline (36.8 g) which melts at 200°—202°C, is prepared by heating 5-amino-6-methoxyisoquinoline (23.5 g), benzoyl chloride (21.1 g) and ammonium thiocyanate (11.5 g) in acetone (360 cc); 5-amino-6-methoxyisoquinoline (22.1 g), which melts at 121°—123°C, is prepared by reducing 6-methoxy-5-nitroisoquinoline (36 g) in water (450 cc) with iron powder (42 g), and 6-methoxy-5-nitroisoquinoline (38.8 g), which melts at 135°—137°C, is prepared by nitrating 6-methoxyisoquinoline (34.2 g) in concentrated sulphuric acid (137 cc) with potassium nitrate 46.7 g.

6-methoxyisoquinoline can be prepared in accordance with the method described by R. Robinson, J. Amer. Chem. Soc., 69, 1939 (1947).

Example 11
A solution of 8-isothiocyanato-1-methyliisoquinoline (28 g) in ethanol (250 cc) at 20°C is added to a solution of ethylenediamine (10 g) in ethanol (250 cc). A white solid precipitate appears after a few minutes. The mixture is stirred for 18 hours at 20°C and the white solid is then filtered off and subsequently washed with ethanol (40 cc).

Yellow mercuric oxide (20 g) is added to the combined ethanolic solutions and the suspension is then heated under reflux for 3 hours. The mercury sulphide which forms is filtered off and then washed with ethanol (40 cc). The filtrates are concentrated to 20 cc. The resulting precipitate is filtered off, washed with diisopropyl ether (40 cc) and dried under reduced pressure (20 mm Hg) at 20°C. The product thus obtained is dissolved in boiling acetonitrile (180 cc). After hot filtration, the solution is cooled at a temperature of about 0°C for 2 hours. The resulting precipitate is filtered off, washed with acetonitrile (10 cc) and dried under reduced pressure (0.1 mm Hg) at 20°C for 15 hours and then at 60°C under this same pressure for 2 hours. 8-(4,5-dihydroimidazol-2-yl)amino-1-methyliisoquinoline (7.9 g), melting at 188°C, is thus obtained.

The 8-isothiocyanato-1-methyliisoquinoline can be prepared in the following manner: 8-amino-1-methyliisoquinoline (33.7 g) is added to a solution of N,N'-thiocarbonyldiimidazole (45.4 g) in methylene chloride (500 cc) at 20°C. The solution is stirred for 20 hours at 20°C. After concentration, the residue is purified by chromatographic filtration on a column (height 53 cm; diameter 5.8 cm) containing silica (700 g), elution being carried out with methylene chloride. The elution fractions containing the purified product are concentrated and the resulting solid is dried under reduced pressure (20 mm Hg) at 20°C. 8-isothiocyanato-1-methyliisoquinoline (28 g), which melts at 50°C, is thus obtained.

8-amino-1-methyliisoquinoline can be obtained by the method of F. A French et al., J. Med. Chem., 13, (6), 1117 (1970).

Example 12
Yellow mercuric oxide (36 g) is added to a solution of ethylenediamine (24.3 g) in ethanol (360 cc) under reflux and a solution of 8-isothiocyanato-7-methyliisoquinoline (20 g) in tetrahydrofuran (50 cc) is then added dropwise in the course of 30 minutes. Reflux is maintained for 1½ hours. The mercury salts are filtered off from the hot reaction mixture. The filtrate is concentrated until a pasty yellow residue is obtained and this is dissolved in boiling acetonitrile (200 cc). Decolourising charcoal (0.5 g) is added and the mixture is filtered hot. A product crystallises from the filtrate on cooling. The crystals are filtered off and dried under reduced pressure (20 mm Hg at 20°C and then 0.1 mm Hg at 60°C). 8-(4,5-dihydroimidazol-2-yl)amino-7-methyliisoquinoline (11.9 g), which melts at 168°C is thus obtained.

8-isothiocyanato-7-methyliisoquinoline can be prepared in the following manner: 8-amino-7-methyliisoquinoline (58.8 g) is added to a solution of N, N'-thiocarbonyldiimidazole (82 g) in methylene chloride (530 cc). The mixture is stirred for 20 hours at 20°C. It is then purified by chromatography on a column (height 75 cm; diameter 5.8 cm) containing silica (1 kg), elution being carried out with methylene chloride. The fractions containing the purified product are concentrated under reduced pressure (20 mm Hg) at 20°C. The resulting solid is dried under reduced pressure (20 mm Hg) at 20°C. 8-isothiocyanato-7-methyliisoquinoline (63.2 g), which melts at 72°C, is thus obtained.

8-amino-7-methyliisoquinoline can be prepared by the method described by E. Brown, J. Org. Chem., 42, 3208 (1977).

Example 13
A solution of 5-isothiocyanato-1-methoxyisoquinoline (9.5 g) and ethylenediamine

(13.2 g) in methylene chloride (200 cc) is stirred at 20°C for 1½ hours. After concentration of the reaction mixture under reduced pressure (20 mm Hg), ethanol (200 cc) and mercuric oxide (8 g) are added to the residue. The suspension is heated under reflux for 45 minutes. After hot filtration, the insoluble material is washed with boiling ethanol (45 cc). After cooling the combined ethanolic solutions at 20°C for 12 hours, the crystals which have appeared are filtered off, washed with ethanol (40 cc) and then with distilled water (60 cc) and dried under reduced pressure (0.2 mm Hg) at 20°C and then at 50°C for a total of 2 hours. 5-(4,5-dihydroimidazol-2-yl)amino-1-methoxyisoquinoline (7.1 g), melting at 214°—215°C, is thus obtained.

The 5-isothiocyanato-1-methoxyisoquinoline can be prepared in the following manner:

A solution of 5-amino-1-methoxyisoquinoline (14.3 g) and N,N'-thiocarbonyldiimidazole (17.5 g) in methylene chloride (500 cc) is stirred at 20°C for 20 hours. The solution is concentrated under reduced pressure (20 mm Hg) and the residue is then chromatographed on a column (height 40 cm; diameter 5 cm) containing silica (380 g), elution being carried out with methylene chloride (2000 cc). The eluate is concentrated under reduced pressure (20 mm Hg). The resulting residue is dried under reduced pressure (20 mm Hg) at 40°C. 5-isothiocyanato-1-methoxyisoquinoline (9.5 g), which melts at 95°—100°C, is thus obtained.

The 5-amino-1-methoxyisoquinoline can be prepared in the following manner:

1-methoxy-5-nitroisoquinoline (17.3 g) in acetic acid (300 cc) is reduced with hydrogen at 30°—45°C under ordinary pressure in the presence of 10% palladium on charcoal (1 g) for 5 hours. The catalyst is filtered off and washed with ethanol (100 cc). The filtrate is concentrated under reduced pressure (20 mm Hg). The resulting residue is taken up in a solution of sodium bicarbonate (15 g) in distilled water (300 cc) for 15 minutes, whilst stirring. The insoluble material is filtered off, washed with distilled water (150 cc) and dried in air at 20°C for 20 hours. 5-amino-1-methoxyisoquinoline (14.3 g), which melts at 56°—60°C, is thus obtained.

1-methoxy-5-nitroisoquinoline can be prepared in the following manner:

A suspension of 1-chloro-5-nitroisoquinoline (20.8 g) and sodium methoxide (12 g) in methanol (500 cc) is heated under reflux for 1½ hours. After cooling, the precipitate is filtered off, washed with methanol (50 cc) and then with distilled water (150 cc) and then dried in air at 20°C for 20 hours. 1-methoxy-5-nitroisoquinoline (17.3 g), which melts at 135°—136°C, is thus obtained.

1-chloro-5-nitroisoquinoline can be prepared in accordance with the method described by B. Elpern, J. Amer. Chem. Soc., 68, 1436 (1946).

Example 14
8-isothiocyanato-5-methylisoquinoline (19.7

65 g) is added to a solution of ethylenediamine (17.7 g) in methylene chloride (500 cc). The mixture is stirred for 20 hours at 20°C. After evaporating off the solvent, the resulting yellow oil is taken up in ethanol (500 cc). The mixture is heated to the reflux temperature and yellow mercuric oxide (20 g) is then added.

After heating under reflux for 1 hour, the mercury salts are filtered off and washed with boiling ethanol (50 cc). The combined ethanolic solutions are evaporated. The resulting yellow solid is taken up in distilled water (100 cc). After filtration, the insoluble material is washed with distilled water (20 cc) and dried under reduced pressure (20 mm Hg) at 20°C. This product is taken up in isopropanol (200 cc) containing 5% of water at boiling point. After hot filtration, the product remaining on the filter is washed with isopropanol (50 cc) containing 5% of water and is then dissolved in 1 N hydrochloric acid (20 cc).

85 After filtration on a glass frit, the solution is neutralised by adding 1 N aqueous sodium hydroxide solution (20 cc). The resulting precipitate is filtered off, washed with water (20 cc) and then dried under reduced pressure (20 mm Hg) at 20°C and then 0.1 mm Hg at 60°C. 8-(4,5-dihydroimidazol-2-yl)amino-5-methylisoquinoline (2.4 g), melting at 261°C, is thus obtained.

The 8-isothiocyanate-5-methylisoquinoline can be prepared in the following manner:

8-amino-5-methylisoquinoline (27 g) is added, at 20°C, to a solution of N,N'-thiocarbonyldiimidazole (32.4 g) in methylene chloride (450 cc). The mixture is stirred for 20 hours at 20°C. The solution is then concentrated and the residue is purified by chromatographic filtration on a column (height 51 cm; diameter 5 cm) containing silica (500 g), elution being carried out with methylene chloride (1 litre). The elution fractions containing the purified product are concentrated and the resulting solid is dried under reduced pressure (20 mm Hg) at 20°C. 8-isothiocyanato-5-methylisoquinoline (19.7 g), which melts at 58°C, is thus obtained.

The 8-amino-5-methylisoquinoline can be prepared in the following manner:

5-methyl-8-nitroisoquinoline (33 g) is added to a suspension of 10% palladium on charcoal (2 g) in acetic acid (400 cc) and a stream of hydrogen is then passed for 5 hours. After filtration on a glass frit filled with a filtering agent, and washing with distilled water (100 cc), the solution is concentrated and the residue is taken up in water (100 cc). The solution is neutralised by adding 1 N aqueous sodium hydroxide solution. The solid which precipitates is filtered off, washed with distilled water (20 cc) and then dried under reduced pressure (20 mm Hg) at 20°C. 8-amino-5-methylisoquinoline (26.6 g), which melts at 136°C, is thus obtained.

5-methyl-8-nitroisoquinoline can be prepared in the following manner:

5-methylisoquinoline (24.8 g) is added in portions to sulphuric acid (d=1.83; 135 cc) which

has been cooled to 0°C. Potassium nitrate (19.2 g) is added in portions, in the course of 1½ hours, to the resulting solution which has been kept at 0°C. Stirring is maintained for 30 minutes at 5°C and then for 1½ hours at 20°C. The mixture is then poured onto ice (600 g), whilst stirring. It is neutralised by adding ammonia solution (d=0.92), whilst cooling at 0°C. This yields a precipitate which is filtered off, washed with water (250 cc) and then dried under reduced pressure (20 mm Hg) at 20°C. 5-methyl-8-nitroisoquinoline (33 g), which melts at 78°C, is thus obtained.

5-methylisoquinoline can be prepared by the method of V. M. Rodionov, Zhur. Obshchei Khim., 27, 734 (1957) [Chem. Abstracts, 51, 16475g (1957)].

Example 15

A solution of 5-isothiocyanato-1-dimethylaminoisoquinoline (10 g) and ethylenediamine (7.8 g) in methylene chloride (200 cc) is stirred at 20°C for 20 hours. The mixture is concentrated under reduced pressure (20 mm Hg), and the resulting residue is then heated under reflux in ethanol (200 cc) in the presence of yellow mercuric oxide (10 g) for 1½ hours. The mercury sulphide is filtered off hot, and the filtrate is left to cool to 20°C. The resulting crystals are filtered off and washed with ethanol (40 cc) and then with distilled water (60 cc). These crystals are dissolved in 2 N hydrochloric acid (50 cc), and decolourising charcoal (0.1 g) is added. After filtration, the solution is tendered alkaline by adding 4 N aqueous sodium hydroxide solution (25 cc). After cooling for 1 hour at 0°C, the precipitate is filtered off, washed with distilled water (60 cc) and then dried under reduced pressure (0.2 mm Hg) at 20°C for 20 hours. 5-(4,5-dihydroimidazol-2-yl)amino-1-dimethylaminoisoquinoline (4.9 g), melting at 215°—216°C, is thus obtained.

The 5-isothiocyanato-1-dimethylaminoisoquinoline can be obtained from 1-chloro-5-nitroisoquinoline. To this effect, 5-isothiocyanato-1-dimethylaminoisoquinoline (10.2 g), which melts at 53°—55°C, is prepared from 5-amino-1-dimethylaminoisoquinoline (9.3 g) and N,N'-thiocarbonyldiimidazole (11 g) in methylene chloride (200 cc); 5-amino-1-dimethylaminoisoquinoline (9.3 g) is prepared in the form of an oil by reducing 1-dimethylamino-5-nitroisoquinoline (12.5 g) in acetic acid (250 cc) with hydrogen in the presence of 10% palladium on charcoal (1 g), and 1-dimethylamino-5-nitroisoquinoline (12.5 g), which melts at 120°C, is prepared by heating 1-chloro-5-nitroisoquinoline (13 g) with dimethylamine (17 g) in acetonitrile (180 cc).

1-chloro-5-nitroisoquinoline can be prepared in accordance with the method described by B. Elpern, J. Amer. Chem. Soc., 68, 1436 (1946).

Example 16

A solution of 8-isothiocyanato-1-

methoxymethylisoquinoline (7.2 g) and ethylenediamine (5.6 g) in methylene chloride (150 cc) is stirred at 20°C for 15 hours. After concentration, ethanol (100 cc) and mercuric oxide (7.5 g) are added to the residue. The mixture is stirred for 2 hours at 20°C, then heated to the reflux temperature and filtered hot and the filtrate is concentrated under reduced pressure (20 mm Hg). The residue is taken up in distilled water (50 cc), the mixture is filtered and the filtrate is concentrated under reduced pressure (20 mm Hg) to a volume of 5 cc. The resulting solid is filtered off and the cake is washed with water (4 cc). The cake is dissolved in 1 N hydrochloric acid (40 cc). The turbid solution is filtered and the filtrate is then rendered alkaline with 1 N aqueous sodium hydroxide solution (40 cc). Extraction is carried out with chloroform (80 cc). After drying over magnesium sulphate (10 g) and filtration, the chloroform extract is concentrated under reduced pressure (20 mm Hg) at 20°C. The residue is taken up in boiling acetonitrile (160 cc). The mixture is filtered hot. After cooling to 20°C, the resulting crystals are filtered off, washed with acetonitrile (20 cc) and dried under reduced pressure (0.1 mm Hg) at 40°C for 2 hours. 8-(4,5-dihydroimidazol-2-yl)amino-1-methoxymethylisoquinoline (2.45 g), melting at 188°—190°C (with decomposition), is thus obtained.

The 8-isothiocyanato-1-methoxymethylisoquinoline can be prepared in the following manner:

A solution of 8-amino-1-methoxymethylisoquinoline (13 g) and N,N'-thiocarbonyldiimidazole (15 g) in methylene chloride (130 cc) is stirred at 20°C for 20 hours. The solution is chromatographed on a column (height 27 cm; diameter 5 cm) containing silica (250 g), elution being carried out with methylene chloride (3000 cc). The eluate is concentrated under reduced pressure (20 mm Hg). 8-isothiocyanato-1-methoxymethylisoquinoline (7.2 g), which melts at 90°C, is thus obtained.

The 8-amino-1-methoxymethylisoquinoline can be prepared in the following manner:

Hydrazine hydrate (58.7 g) is added, in the course of 30 minutes, to a solution of 5-bromo-1-methoxymethyl-8-nitroisoquinoline (28.6 g) in ethanol (570 cc) under reflux, 4% palladium on charcoal (6 g) having been added to this solution. Reflux is maintained for 2 hours after the addition has been completed. After filtering off the catalyst, the alcoholic solution is concentrated under reduced pressure (20 mm Hg). The residue is extracted with a mixture of water (50 cc) and diethyl ether (100 cc). The organic phase which is dried in the presence of magnesium sulphate (15 g) and then filtered, is concentrated under reduced pressure (20 mm Hg). 8-amino-1-methoxymethylisoquinoline (17 g), which melts at 72°—75°C, is thus obtained.

The 5-bromo-1-methoxymethyl-8-nitroisoquinoline can be prepared in the following manner:

Potassium nitrate (11.4 g) is added in portions to a solution, which has been cooled to 0°C, of 5-bromo-1-methoxymethylisoquinoline (26 g) in concentrated sulphuric acid (120 cc). After the addition has been completed, the temperature is kept at 0° for 30 minutes and then at 20°C for 1½ hours. The mixture is then poured onto crushed ice (600 g) and neutralised with 11 N ammonia solution (400 cc). The resulting precipitate is filtered off and the cake is washed with distilled water (400 cc) and dried in air for 20 hours. 5-bromo-1-methoxymethyl-8-nitroisoquinoline (28.6 g), which melts at 136°—137°C, is thus obtained.

15 The 5-bromo-1-methoxymethylisoquinoline can be prepared in the following manner:
A mixture of 5-bromo-1-bromomethylisoquinoline (40 g) and sodium methoxide (12 g) in methanol (400 cc) is heated under reflux for 30 minutes. The solution obtained is concentrated and the residue is taken up in distilled water (100 cc). The resulting precipitate is filtered off and the cake is washed with distilled water (100 cc) and dried at 20°C under reduced pressure (0.2 mm Hg). 5-bromo-1-methoxymethylisoquinoline (26.2 g), which melts at 72°C, is thus obtained.

20 The 5-bromo-1-bromomethylisoquinoline can be prepared in the following manner:
A mixture of 5-bromo-1-methylisoquinoline (89 g), N-bromosuccinimide (125 g) and benzoyl peroxide (4.5 g) in carbon tetrachloride (2200 cc) is heated under reflux for 16 hours. The resulting suspension is filtered and the cake is washed with carbon tetrachloride (400 cc). The filtrate is poured onto a column (diameter 9.5 cm; height 32 cm) containing silica (1000 g). Elution is carried out with methylene chloride (1600 cc). The eluate is concentrated under reduced pressure. 5-bromo-1-bromomethylisoquinoline (55 g), which melts at 116°—117°C, is thus obtained.

25 The 5-bromo-1-methylisoquinoline can be prepared in the following manner:
Anhydrous aluminium chloride (226 g) is added in small portions, in the course of 30 minutes, to 1-methylisoquinoline (117 g), the temperature of the reaction medium changing from 30° to 120°C. After cooling to a temperature of about 80°C, bromine (28.7 cc) is added in the course of 2½ hours and the same temperature is maintained for a further 2 hours. After cooling to a temperature of about 20°C, the reaction medium is poured onto crushed ice (2.5 kg). 10 N aqueous sodium hydroxide solution (900 cc) is then added. The product which partially precipitates is extracted with diethyl ether (1.5 litres and then 2 x 500 cc). The combined organic layers are dried over magnesium sulphate. After filtration and concentration to dryness, the residue is washed on a filter with hexane (500 cc and then 5 x 100 cc) and dried under reduced pressure. 5-bromo-1-methylisoquinoline (86.5 g), which melts at 98°C, is thus obtained.

70 The washings are concentrated to dryness and the residue is taken up in hexane (100 cc). The insoluble material is filtered off, washed with petroleum ether (3 x 50 cc) and then dried. 5-Bromo-1-methylisoquinoline (21 g), which melts at 94°C, is thus obtained.

Example 17

75 Yellow mercuric oxide (20.7 g) is added to ethylene diamine (10 g) in anhydrous ethanol (350 cc). The mixture is heated to the reflux temperature and a solution of 8-isothiocyanato-1,5-dimethylisoquinoline (6.2 g) in tetrahydrofuran (60 cc) is added dropwise. Reflux is maintained for 1½ hours. The mixture is filtered hot in order to separate off the mercury salts and they are washed with boiling ethanol (50 cc). The ethanolic solutions are concentrated and the residue is taken up in distilled water (200 cc). The insoluble product is filtered off and washed with water (50 cc). The filtrate is acidified to pH 3 with 11 N hydrochloric acid and then treated with decolourising charcoal. The filtrate is brought to a pH of about 9 by adding 10 N aqueous sodium hydroxide solution. Extraction is carried out with methylene chloride (500 cc). The methylene chloride extract is dried over sodium sulphate and then concentrated. The resulting yellow solid is chromatographed on a column (height 13 cm; diameter 1.5 cm) containing alumina (20 g) and eluted with methylene chloride. The elution fractions containing the product are concentrated to dryness. The residue is taken up in a minimum amount of boiling isopropanol. This yields a solution which is treated with decolourising charcoal. After filtration, the filtrate is left to cool and crystallisation is started by scratching. After standing for a few hours at 0°C, the crystals are filtered off, washed with diethyl ether (5 cc) and dried under reduced pressure. The crystals are taken up in boiling acetonitrile (20 cc) and the solution is treated with decolourising charcoal and then filtered hot. The filtrate is cooled to about 20°C and crystallisation is then started. After standing for several hours at 20°C, the crystals are filtered off and washed with acetonitrile (2 cc). The resulting product is dried under reduced pressure (20 mm Hg at 20°C and 0.5 mm Hg at 60°C). 8-(4,5-dihydroimidazol-2-yl)-amino-1,5-dimethylisoquinoline (0.7 g), melting at 182°C, is thus obtained.

90 The 8-isothiocyanato-1,5-dimethylisoquinoline can be prepared in the following manner:
N,N'-thiocarbonyldiimidazole (8 g) is added to 8-amino-1,5-dimethylisoquinoline (6.4 g) in methylene chloride (100 cc). The mixture is stirred for 20 hours at 20°C. The reaction mixture is concentrated to dryness and the residue is purified by chromatography on a column (height 24.5 cm; diameter 2.7 cm) containing silica (70 g), elution being carried out with methylene chloride. The fractions containing the purified product are concentrated to dryness. The resulting solid is dried under reduced pressure (20 mm Hg) at 20°C. 8-isothiocyanato-1,5-

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dimethylisoquinoline (6.2 g), which melts at 124°C, is thus obtained.

The 8-amino-1,5-dimethylisoquinoline can be prepared in the following manner:

5 10% palladium on charcoal (2 g) is added to a solution of 1,5-dimethyl-8-nitroisoquinoline (8.2 g) in acetic acid (70 cc). After having purged the apparatus with nitrogen, a stream of hydrogen is bubbled into the suspension. The mixture is stirred 10 under these conditions for 3 hours. The apparatus is then purged with nitrogen. The mixture is filtered and the filtrate is concentrated to dryness. The residue is taken up in ice-cooled water (500 cc) and the pH is brought to about 8 by adding 10 N ammonia solution. The mixture is left to stand for 2 hours at 0°C and the crystals which have appeared are filtered off and washed with water (45 cc). After drying in air and then under reduced pressure (20 mm Hg) at 20°C, 8-amino-1,5-dimethylisoquinoline (6.4 g), which melts at 158°C, is obtained.

The 1,5-dimethyl-8-nitroisoquinoline can be prepared in the following manner:

Potassium nitrate (20.8 g) is added in small amounts, in the course of 3 hours, to a solution of 1,5-dimethylisoquinoline (28.8 g) in concentrated sulphuric acid (140 cc). The mixture is stirred for 2 hours at 20°C. The solution is then poured onto crushed ice (2 kg) and neutralized by adding 10 N ammonia solution. A brown product precipitates and is filtered off, washed with distilled water (400 cc), dried in air and then taken up in diethyl ether (2 litres). The insoluble material is filtered off and the filtrate is concentrated to dryness. The residue is vigorously stirred with diisopropyl ether (30 cc). The insoluble material is filtered off and then dried under reduced pressure (20 mm Hg) at 20°C, 1,5-dimethyl-8-nitroisoquinoline (18.4 g), which melts at 120°C, is thus obtained.

1,5-dimethylisoquinoline can be obtained by the method of Ernst Späth *et al.*, *Ber.*, 63B, 134-141 (1930).

Example 18

Ethylenediamine (6 cc) is added to a solution of 8-isothiocyanato-5-methylthioisoquinoline (6.7 g) in methylene chloride (100 cc) and the mixture is stirred for 20 hours at 20°C. After concentration of the reaction mixture, the residue is taken up in ethanol (100 cc). The mixture is heated to the reflux temperature, yellow mercuric oxide (7 g) is added and reflux is maintained for 3 minutes. The reaction mixture is then stirred for a further 30 minutes whilst allowing the temperature to return to about 20°C. The mixture is again heated to the reflux temperature and the mercury salts are filtered off from the hot mixture and washed with ethanol (20 cc). The ethanolic solutions are concentrated. The residue is vigorously stirred with water (50 cc). The insoluble material is filtered off, washed with water (30 cc) and then taken up in boiling acetonitrile (250 cc). After hot filtration and cooling the filtrate, a yellow product crystallises. The crystals are filtered off, washed with acetonitrile (30 cc) and dried under reduced pressure (20 mm Hg) at 20°C, 8-isothiocyanato-5-methylthioisoquinoline (3.4 g), melting at 212°-214°C, is thus obtained.

The 8-isothiocyanato-5-methylthioisoquinoline can be prepared in the following manner:

N,N'-thiocarbonyldiimidazole (8.2 g) is added to a solution of 8-amino-5-methylthioisoquinoline (6.5 g) in methylene chloride (100 cc) and the mixture is stirred for 20 hours at 20°C. After evaporating off the solvent, the residue is chromatographed on a column (height 32 cm; diameter 3.5 cm) containing silica (110 g). Elution is carried out with methylene chloride. The fractions containing the purified product are combined and concentrated to dryness. The resulting product is dried under reduced pressure (20 mm Hg) at 20°C. 8-isothiocyanato-5-methylthioisoquinoline (6.7 g), which melts at 124°C, is thus obtained.

Example 19

Ethylenediamine (0.8 cc) is added to a solution of 8-isothiocyanato-5,7-dimethylthioisoquinoline (1 g) in methylene chloride (50 cc). The mixture is stirred for 20 hours at 20°C. After concentration of the reaction mixture, the residue is taken up in ethanol (50 cc). The mixture is then heated to the reflux temperature and yellow mercuric oxide (1 g) is added. Reflux is maintained for 3 minutes, and the mixture is then stirred for a further 30 minutes whilst allowing the temperature to return to about 20°C. The mixture is again heated to the reflux temperature and the mercury salts are filtered off hot and washed with ethanol (10 cc). The ethanolic solutions are concentrated to dryness. The residue is taken up in water (20 cc). The insoluble material is filtered off, washed with water (30 cc) and dried under reduced pressure (20 mm Hg) at 20°C. 8-(4,5-dihydroimidazol-2-yl)amino-5,7-dimethylthioisoquinoline (0.85 g), melting at 206°C, is thus obtained.

The 8-isothiocyanato-5,7-dimethylthioisoquinoline can be prepared in the following manner:

N,N'-thiocarbonyldiimidazole (1.95 g) is added to a solution of 8-amino-5,7-dimethylthioisoquinoline (2 g) in methylene chloride (30 cc). The mixture is stirred for 20 hours at 20°C. After evaporating off the solvent, the residue is chromatographed on a column (height 20 cm; diameter 3 cm) containing silica (50 g), elution being carried out with methylene chloride. The fractions containing the purified product are combined and concentrated. The resulting product is dried under reduced pressure (20 mm Hg) at 20°C. 8-isothiocyanato-5,7-dimethylthioisoquinoline (1 g), which melts at 144°C, is thus obtained.

8-amino-5-methylthioisoquinoline and the 8-amino-5,7-dimethylthioisoquinoline can be prepared in the following manner:

Methylmercaptan is bubbled at 0°C, up to the saturation point, into ethanol (125 cc) containing sodium methoxide (12.7 g). 5-bromo-8-

nitroisoquinoline (24.1 g) is added. The mixture is stirred for 16 hours at 20°C and then heated under reflux for 20 minutes. After evaporating off the solvent, the residue is taken up in methylene chloride (200 cc) and distilled water (200 cc), whilst stirring vigorously at the same time. The organic phase is decanted and the aqueous layer is extracted with methylene chloride (200 cc).

The combined organic layers are washed with water (200 cc) and dried over magnesium sulphate. After concentrating the solvent, the residue is chromatographed on a column (height 25 cm; diameter 5 cm) containing silica (250 g), elution being carried out in fractions (250 cc), firstly with methylene chloride (5 litres) and then with a methylene chloride/methanol mixture (1 litre) containing 2% of methanol. These fractions are concentrated to dryness and the product is dried under reduced pressure (20 mm Hg) at 20°C. 8-amino-5,7-dimethylthioisoquinoline (7.1 g), which melts at 120°C, is thus obtained.

By continuing elution with a methylene chloride/methanol mixture (1.5 litres) containing 4% of methanol, concentrating to dryness and drying under reduced pressure (20 mm Hg) at 20°C, 8-amino-5-methylthioisoquinoline (6.5 g), which melts at 126°C, is obtained.

Example 20

A mixture of methyl isoquinol-5-ylidithiocarbamate (4.68 g) and ethylenediamine (3.6 g) in ethanol (100 cc) is heated under reflux for 1½ hours. Mercuric oxide (5 g) is then added and the mixture is again heated under reflux for 3½ hours. After hot filtration, the filtrate is concentrated under reduced pressure (20 mm Hg). The resulting residue is taken up in distilled water (30 cc), whilst stirring for 1 hour. The insoluble material is filtered off, washed with distilled water (30 cc) and then dried under reduced pressure (0.2 mm Hg) at 20°C. 5-(4,5-dihydroimidazol-2-yl)aminoisoquinoline (2.6 g), which melts at 191°—192°C, is thus obtained.

The methyl isoquinol-5-ylidithiocarbamate can be prepared in the following manner:

A solution of methyl iodide (15.6 g) in acetonitrile (25 cc) is added dropwise to a suspension of triethylammonium isoquinol-5-ylidithiocarbamate (32.1 g) in acetonitrile (100 cc), the temperature being kept at 30°—35°C.

Heating is continued for 1½ hours after the addition has been completed. Water (200 cc) and methylene chloride (200 cc) are added to the reaction medium. The solid which precipitates is filtered off and washed with methylene chloride (60 cc) and then with water (60 cc). It is dried at 20°C under reduced pressure (0.2 mm Hg) for 20 hours. Methyl isoquinol-5-ylidithiocarbamate (12.2 g), which melts at 188°C, is thus obtained.

The triethylammonium isoquinol-5-ylidithiocarbamate can be prepared in the following manner:

Carbon disulphide (56.7 g) is added dropwise to a suspension of 5-aminoisoquinoline (72 g) in acetonitrile (90 cc) and triethylamine (50.5 g),

65 whilst heating at 30°C. After cooling to 0°C, the resulting crystalline solid is filtered off and the cake is washed with diethyl ether (200 cc) and dried at 20°C under reduced pressure (0.2 mm Hg).

70 Triethylammonium isoquinol-5-ylidithiocarbamate (132 g), which melts at 142°C, is thus obtained.

Example 21

A solution of bromine (2.88 g) in acetic acid (10 cc) is added dropwise, at 20°C, to 8-(4,5-dihydroimidazol-2-yl)amino-5-methylisoquinoline (4.08 g) in acetic acid (25 cc). A yellow solid precipitates; it is filtered off and washed with acetic acid (10 cc).

This solid is dissolved in water (100 cc). An insoluble material is removed by filtration. The filtrate is neutralised by adding 1 N aqueous sodium hydroxide solution until the pH is 7—8. The resulting precipitate is stirred for 1 hour at 0°C and is then filtered off, washed with water (20 cc) and finally dried under reduced pressure (20 mm Hg) at 20°C.

The resulting product (3.8 g) is dissolved in isopropanol (150 cc) containing 5% of water at the boiling point. The solution is filtered hot and then cooled to 5°C. The crystalline product is filtered off, washed with isopropanol (10 cc) and dried under reduced pressure (20 mm Hg at 20°C and then 0.1 mm Hg at 60°C). 7-bromo-8-(4,5-dihydroimidazol-2-yl)amino-5-methylisoquinoline (2.4 g), melting at 282°—283°C, is thus obtained.

In the foregoing Examples where there is no temperature indicated the operation involved is carried out at about 20°C.

100 The present invention includes within its scope pharmaceutical compositions comprising, as active ingredient, at least one of the compounds of general formula I or a non-toxic acid addition salt therof, in association with a pharmaceutical carrier or coating. The invention includes especially such preparations made up for oral or parenteral administration.

Solid compositions for oral administration include tablets, pills, powders and granules. In 110 such solid compositions the active compound is admixed with at least one inert diluent such as sucrose, lactose or starch. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g.

115 lubricating agents, such as magnesium stearate. Liquid compositions for oral administration include pharmaceutically-acceptable solutions, suspensions syrups and elixirs containing inert diluents commonly used in the art, such as water or liquid paraffin. Besides inert diluents such

120 compositions may also comprise adjuvants, such as wetting, emulsifying and suspending agents, and sweetening, flavouring and aromatizing agents. The compositions according to the invention, for oral administration, also include capsules of absorbable material such as gelatin containing the active substance with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as preserving, wetting, emulsifying and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilizing agents, by irradiation, or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage depends on the desired therapeutic effect, on the route of administration and on the duration of the treatment. The compositions are particularly useful in human therapy in the treatment of hypertension. In human therapy the compositions when administered orally to an adult should generally give doses between 4 mg and 200 mg of active substance per day in one or more doses. In general the physician will decide the posology considered appropriate, taking into account the age and weight and other factors intrinsic to the patient being treated.

35 The following Examples illustrate pharmaceutical compositions according to the invention.

Example 22

Tablets containing a 25 mg dose of active product and having the following composition are prepared in accordance with the usual technique:

	g
5-[4,5-dihydroimidazol-2-yl]amino]-6-methoxyisoquinoline	0.025
starch	0.200
precipitated silica	0.020
magnesium stearate	0.005

Example 23

50 Tablets containing a 25 mg dose of active product and having the following composition are prepared in accordance with the usual technique:

	g
8-[4,5-dihydroimidazol-2-yl]amino]-1-methylisoquinoline	0.025
starch	0.200
precipitated silica	0.020
magnesium stearate	0.005

60 Example 24

Tablets containing a 25 mg dose of active

product and having the following composition are prepared in accordance with the usual technique:

	g
65 4-(4,5-dihydroimidazol-2-yl)aminoisoquinoline	0.025
starch	0.200
precipitated silica	0.020
magnesium stearate	0.005

70 Claims

1. Isoquinoline derivatives of the general formula:



(wherein R₁ represents a hydrogen atom or a hydroxyalkyl radical containing 1 to 4 carbon atoms, the imidazolin-2-ylamino group is attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus, and the symbols R₂ and R₃, which have the same or different significances, are attached to carbon atoms in the remaining positions of the isoquinoline nucleus and each represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkoxyalkyl group in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms, or a dialkylamino group in which each alkyl radical contains 1 to 4 carbon atoms) and acid addition salts thereof.

2. Isoquinoline derivatives according to Claim 1 wherein R₁ and R₂ are as defined in Claim 1, and R₃ represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms or an alkylthio radical containing 1 to 4 carbon atoms, and acid addition salts thereof.

3. Isoquinoline derivatives according to Claim 1 wherein R₁ is as defined in Claim 1, and the symbols R₂ and R₃, which have the same or different significances, each represents a hydrogen or halogen atom or an alkyl radical containing 1 to 4 carbon atoms, and acid addition salts thereof.

4. Isoquinoline derivatives according to Claim 1 wherein R₁ represents a hydrogen atom, and the symbols R₂ and R₃, which have the same or different significances, each represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms, and acid addition salts thereof.

5. Isoquinoline derivatives according to Claim 1 wherein R₁ represents a hydrogen atom or a 2-hydroxyethyl group and the symbols R₂ and R₃, which have the same or different significances, each represents a hydrogen, chlorine or bromine atom, or a methyl, methoxy, methoxymethyl or methylthio radical, or a dimethylamino group, and acid addition salts thereof.

6. Isoquinoline derivatives according to any

one of the preceding claims in which the imidazolin-2-ylamino group in the general formula depicted in Claim 1 is attached to the 4-, 5- or 8-position of the isoquinoline nucleus, and acid addition salts thereof.

5 7. 4-(4,5-dihydroimidazol-2-yl)aminoisoquinoline and acid addition salts thereof.

8. 8-(4,5-dihydroimidazol-2-yl)aminoisoquinoline and acid addition salts thereof.

10 9. 8-(4,5-dihydroimidazol-2-yl)amino-1-methylisoquinoline and acid addition salts thereof.

15 10. 8-(4,5-dihydroimidazol-2-yl)amino-7-methylisoquinoline and acid addition salts thereof.

11. 8-(4,5-dihydroimidazol-2-yl)amino-5-methylisoquinoline and acid addition salts thereof.

20 12. 5-(4,5-dihydroimidazol-2-yl)aminoisoquinoline, 5-(4,5-dihydroimidazol-2-yl)amino-3-methylisoquinoline, 5-[1-(2-hydroxyethyl)-4,5-dihydroimidazol-2-yl]aminoisoquinoline, 5-(4,5-dihydroimidazol-2-yl)amino-3,4-dimethylisoquinoline, 7-(4,5-dihydroimidazol-2-yl)aminoisoquinoline, 6-(4,5-dihydroimidazol-2-yl)aminoisoquinoline and 6-chloro-5-(4,5-dihydroimidazol-2-yl)aminoisoquinoline, and acid addition salts of each such compound.

13. 5-(4,5-dihydroimidazol-2-yl)amino-6-methoxyisoquinoline, 5-(4,5-dihydroimidazol-2-yl)amino-1-methoxyisoquinoline, 5-(4,5-dihydroimidazol-2-yl)amino-1-dimethylaminoisoquinoline, 8-(4,5-dihydroimidazol-2-yl)amino-1-methoxymethylisoquinoline, 8-(4,5-dihydroimidazol-2-yl)amino-1,5-dimethylisoquinoline, 8-(4,5-dihydroimidazol-2-yl)amino-5-methylthioisoquinoline, 8-(4,5-dihydroimidazol-2-yl)amino-5,7-dimethylthioisoquinoline and 7-bromo-8-(4,5-dihydroimidazol-2-yl)amino-5-methylisoquinoline, and acid addition salts of each such compound.

14. A process for the preparation of an isoquinoline derivative as claimed in Claim 1 which comprises reacting an ethylenediamine of the general formula:

50
$$\text{H}_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}-\text{R}_1 \quad (\text{II})$$

(wherein R_1 is as defined in Claim 1) with an isoquinoline derivative of the general formula:

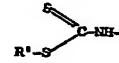
55
$$\text{R}_2-\text{X}-\text{R}_3 \quad (\text{III})$$

wherein R_2 and R_3 are as defined in Claim 1 and X attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus represents (i) a 2-alkylisothioureido group of the general formula:



(IV)

60 or (ii) an (alkylthio)-thiocarbonylamino group of the general formula:

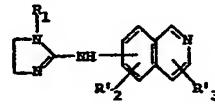


(V)

[wherein R' in general formulae (IV) and (V) represents an alkyl radical containing 1 to 4 carbon atoms], or (iii) the isothiocyanato radical.

65 15. A process according to Claim 14 in which Z in general formula (III) represents a 2-alkylisothioureido group of general formula (IV) and the isoquinoline reactant is employed in the form of a salt with an inorganic or organic acid.

70 16. A process for the preparation of an isoquinoline derivative as claimed in Claim 1 wherein R_1 represents a hydrogen atom or a hydroxylalkyl radical containing 1 to 4 carbon atoms, the imidazolin-2-ylamino group is attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus, and one of the symbols R_2 and R_3 represents a halogen atom and the other represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkoxyalkyl radical in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms or a dialkylamino group in which each alkyl radical contains 1 to 4 carbon atoms, which comprises reacting a halogenating agent with an isoquinoline derivative of the general formula:



(XI)

90 wherein R_1 is as defined in Claim 1, the imidazolin-2-ylamino group is attached to the 4-, 5-, 6-, 7- or 8-position of the isoquinoline nucleus, and one of the symbols R'_2 and R'_3 attached to a carbon atom in a remaining position of the isoquinoline nucleus represents a hydrogen atom and the other attached to a carbon atom represents a hydrogen or halogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, an alkoxyalkyl radical in which the alkyl and alkoxy moieties each contain 1 to 4 carbon atoms, an alkylthio radical containing 1 to 4 carbon atoms or a dialkylamino group in which each alkyl radical contains 1 to 4 carbon atoms, it being understood that, when the symbols R'_2 and R'_3 each represent a hydrogen atom, two halogen atoms can be introduced onto the isoquinoline nucleus.

95 17. A process according to Claim 16 in which the halogenating agent is chlorine or bromine.

100 18. A process according to any one of Claims 14 to 17 followed by the step of converting the resulting isoquinoline derivative by known methods into an acid addition salt.

105 19. A process for the preparation of an

isoquinoline derivative of the general formula specified in Claim 1 and acid addition salts thereof substantially as hereinbefore described with especial reference to any one of Examples 1 to 9.

5 20. A process for the preparation of an isoquinoline derivative of the general formula specified in Claim 1 and acid addition salts thereof substantially as hereinbefore described in any one of Examples 10 to 21.

10 21. Isoquinoline derivatives of the general formula specified in Claim 1 and acid addition salts thereof when prepared by the process claimed in any one of Claims 14 to 20.

15 22. Pharmaceutical compositions which comprises as active ingredient at least one isoquinoline derivative as claimed in any one of Claims 1 to 13, or a non-toxic acid addition salt thereof, in association with at least one compatible pharmaceutically acceptable carrier.

20 23. Pharmaceutical compositions according to Claim 22 substantially as hereinbefore described with especial reference to Example 22, 23 or 24.

24. An isoquinoline derivative as claimed in any one of Claims 1 to 13, or a non-toxic acid addition salt thereof, when used as a medicament and, more particularly, for the treatment of hypertension.

25

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